Albuminuria in Diabetes Mellitus

Relation to Ambulatory Versus Office Blood Pressure and Effects of Cilazapril

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This study aimed to investigate the relationship between microalbuminuria and office blood pressure (BP) as compared with ambulatory BP in patients with diabetes mellitus under everyday practice conditions. It was also undertaken to assess the effect of the angiotensin converting enzyme inhibitor cilazapril on diabetes-associated albuminuria. Ambulatory BP was recorded during daytime in 54 patients with type II diabetes mellitus at the end of a 4-week period during which they received no vasoactive drug. The difference between office and ambulatory BP was unpredictable in the individual patient. There was no significant correlation between either ambulatory or office BP and urinary albumin/creatinine ratio. Fifty-one patients underwent a 40-week treatment with 5 mg/day of cilazapril. There was, in the absence of satisfactory BP control, the possibility of adding the calcium antagonist amlodipine (5 mg/day) from the 10th week onward and 12.5 mg/day of hydrochlorothiazide from the 20th week onward. Office mean BP was significantly reduced after 30 to 40 weeks of therapy in patients with normoalbuminuria (n = 19, −14%, $P < .001$), in those with microalbuminuria (n = 22, −6.6%, $P < .01$), as well as in those with clinical proteinuria (n = 9, −11.4%, $P < .01$). During the same time, the urinary albumin/creatinine ratio was not modified in normoalbuminuric patients (n = 19, +24.6%, $P = .72$) as well as in those with clinical proteinuria (n = 9, −29.4%, $P = .09$). On the other hand this value was significantly reduced for the group with microalbuminuria (n = 23, −24.3%, $P < .05$). In the overall population, as well as in hyperalbuminuric patients (patients with microalbuminuria + patients with clinical proteinuria), the reduction of the albumin/creatinine ratio was also significant (n = 51, −7%, $P < .01$ and n = 32, −25,7%, $P < .01$, respectively). In conclusion, the findings of this study performed by practicing physicians show that ambulatory BP may differ greatly from office BP in diabetic patients. They also indicate that urinary albumin excretion is poorly correlated with office and ambulatory BP in type II diabetics. Finally, they demonstrate the antiproteinuric action of prolonged treatment with the angiotensin converting enzyme inhibitor cilazapril, whether given alone or combined with amlodipine. © 1996 American Journal of Hypertension, Ltd. **Am J Hypertens 1996;9:1220–1227**

KEY WORDS: **Hypertension, angiotensin converting enzyme inhibition, calcium antagonist, diuretic, diabetic nephropathy.**

In Europe more than 25 million persons may have diabetes mellitus, 10% of them insulin dependent (type I) and 90% primary non–insulin-dependent (type II) diabetes mellitus. About 35% of type I and 25% of type II diabetics develop nephropathy.[1] This complication manifests itself 7 to 15 years after the onset of diabetes mellitus (in diabetes mellitus type II seemingly earlier) as persistent microalbuminuria (incipient ne-

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phropathy).[2] In its natural course, microalbuminuria progresses in 80% to 100% of cases within 10 to 30 years from diabetes mellitus onset to proteinuria of >0.3 g/day and glomerular filtration rate now begins to decrease (clinical nephropathy). And the latter progresses in 90% rather rapidly, within 10 years to terminal renal failure. Not only has diabetes mellitus emerged as the most common cause of end-stage kidney disease,[3] but relative cardiovascular mortality is increased up to sixfold in diabetics with hypertension and/or microalbuminuria [4–6] and up to a staggering 35-fold once the latter has progressed to clinical nephropathy.[7,8]

Diabetes mellitus-associated metabolic changes and glomerular hypertension are thought to promote diabetic nephropathy.[9,10] Intraglomerular pressure depends in part on systemic blood pressure (BP). In diabetes mellitus type I, BP tends to rise slightly, although still within the normal range, before or concomitant with the onset of incipient nephropathy.[11,12] Thus, positive correlations between urinary albumin excretion and clinic BP have been noted in type I diabetes mellitus.[11,13] In diabetes mellitus type II, systemic hypertension often exists already years before the appearance of diabetes mellitus or nephropathy.[1,14] Because office BP is often distorted by a "white-coat" pressor effect, ambulatory BP has been found to be more predictive of cardiovascular complications[15–18] and perhaps could also correlate better with diabetic albuminuria.

In reducing microalbuminuria or clinical proteinuria, certain angiotensin converting enzyme (ACE) inhibitors have been more effective than other antihypertensive agents.[19,20] Considering this state of information, which has been based largely on studies performed in specialized investigation centers, the present study was undertaken to evaluate the following questions: 1) to what extent are office BP readings in type II diabetic patients with hypertension or microalbuminuria predictive of their mean daytime ambulatory BP? 2) what is the relationship of type II diabetes mellitus-associated albuminuria observed under nonspecialized, everyday practice conditions with office BP as compared to ambulatory BP? and 3) what is the efficacy of the newer long-acting ACE inhibitor cilazapril in reducing type II diabetes mellitus-associated hyperalbuminuria?

PATIENTS AND PROTOCOL

Patients were enrolled by their treating physicians in private practice. Men and women, aged 18 to 75 years, with type II diabetes mellitus and on standard antidiabetic therapy (dietary instruction and oral antidiabetic agents or insulin where appropriate) were considered eligible. An initial clinical examination including retinoscopy, a standard 12-lead electrocardiogram, and measurement of urinary albumin/creatinine ratio in a spot urine were performed. Patients who were either diagnosed as 1) hypertensive (based on repeated office BP > 140/90 mm Hg and/or the history of ongoing antihypertensive treatment), or 2) normotensive (office BP ≤ 140/90 mm Hg) but having an increased urinary albumin excretion (albumin/creatinine ratio < 2.27 mg/mmol in the spot urine), entered the study.

All these patients underwent a 4-week observation period, during which they received no vasoactive drugs ("wash-out" period). During the last 2 weeks, urine spots were collected again two to three times for determination of albumin/creatinine ratio. The mean of these measurements was calculated. Office BP, daytime ambulatory BP profiles, and various laboratory parameters (see below) also were determined at the end of the wash-out period. The study was subdivided into two parts (Table 1). Study A comprised all patients in whom at the end of the wash-out period ambulatory BP monitoring could be successfully performed and analyzed. The aim of this study part was to assess the relationships among ambulatory BP, office BP, and albuminuria in type II diabetics off antihypertensive drugs. The study B examined the effects of the active antihypertensive drug therapy on these variables and involved all patients exhibiting at the end of the 4-week run-in period an elevated ambulatory or, in the absence of an interpretable ambulatory profile, office diastolic BP > 90 mm Hg or confirmed elevated albuminuria.

Exclusion criteria were severe hypertension (mean ambulatory or office diastolic BP > 115 mm Hg) or malignant hypertension, secondary forms of hypertension (except hypertension associated with diabetes mellitus per se), type I diabetes, decompensated diabetes mellitus, proliferative diabetic retinopathy, myocardial infarction, congestive heart failure, stroke, nephropathy of nondiabetic origin, serum creatinine > 160 μmol/L, kalemia > 5 mmol/L, pregnancy or lactation, drug or alcohol abuse, suspected noncompliance with treatment, and severe illnesses such as chronic hepatitis, liver cirrhosis, or cancer.

The active treatment period lasted 40 weeks. Blood pressure was monitored at 10-week intervals at the office and whenever possible by ambulatory BP monitoring. During the first 10 weeks, the ACE inhibitor cilazapril was administered in a dose of 5 mg once daily. During weeks 11 to 20, patients with a mean ambulatory diastolic daytime BP of < 85 mm Hg or, in the absence of interpretable ambulatory data, an office diastolic BP of ≤ 90 mm Hg continued on cilazapril monotherapy, 5 mg daily, whereas patients whose BP was still elevated (according to either ambulatory or office BP values) received cilazapril, 5 mg, combined with the calcium antagonist amlodipine, 5 mg, once daily. From week 21 to 40, patients who at week 20 were normotensive (according to the criteria described above) continued their previous medication, whereas those who were still hypertensive received in addition hydrochlorothiazide, 12.5 mg once daily. Determinations of urinary albumin/creatinine ratio were performed at 10-week intervals. The means of measurements at the end of the wash-out phase were used as basal pretreatment values whereas the mean of measurements

TABLE 1. STUDY PROTOCOL AND DEMOGRAPHICS IN TYPE II DIABETICS WITH HYPERTENSION* AND/OR HYPERALBUMINURIA†

	Study A	Study B
Inclusion criteria after ≥4 weeks without vasoactive drugs	Technically satisfactory ambulatory BP monitoring	Hypertension* or hyperalbuminuria† or both
Study aim	To assess relationships among ambulatory BP, office BP, and albuminuria in type II diabetics off vasoactive drugs	To assess effects of 40 weeks of treatment with ACE inhibitor cilazapril and, if necessary, added amlodipine and hydrochlorothiazide, on BP, albuminuria, and some additional variables
Patients completing study:		
No.	54	51
Age (years)	56 ± 1.5	57 ± 1.4
Sex distribution (F/M)	15/39	15/36
Known duration of diabetes (years)	8.4 ± 1.1	9.1 ± 1.1
Body weight (kg)	84.5 ± 2.2	84.3 ± 2.3

ACE, angiotensin converting enzyme, BP, blood pressure

** Mean daytime ambulatory diastolic BP ≥85 mm Hg or seated office diastolic BP >90 mm Hg; † Urinary albumin/creatinine ratio ≥2.27 mg/mmol. Data shown as means ± SEM*

after active treatment weeks 30 and 40 were used as final values.

At completion of the run-in phase and again after 10 and 40 weeks of active treatment, fasting serum glucose, glycosylated hemoglobin (HbA_{1c}), fructosamine, total cholesterol, HDL cholesterol, triglycerides, sodium, potassium, creatinine, transaminase and alkaline phosphatase levels, hemoglobin and white blood cell count were measured. Fasting C-peptide for verification of diabetes mellitus type was determined at baseline. At the end of the study, clinical examinations, retinoscopy, and standard 12-lead electrocardiogram were repeated.

Analytical Methods Office BP was determined after 5 min in the seated position by the conventional auscultatory method using a sphygmomanometer and a pressure cuff. The fifth sound was defined as diastolic BP. Ambulatory BP monitoring was performed with the device Profilomat (Disetronic, Burgdorf, Switzerland), a fully automated apparatus. This ambulatory recorder has been validated according to the protocol of the British Hypertension Society, receiving the best grade for diastolic and the second best grade for systolic BP.[21] Participating physicians attended preparatory training sessions where they were instructed to 1) place the cuff over the previously palpated brachial artery, 2) always take three auscultatory control readings with a sphygmomanometer connected simultaneously to the cuff, and 3) systematically validate the method by ascertaining before each BP monitoring that the average diastolic and systolic differences between readings by the recorder and control measurements were < 5 mm Hg. The patients were asked to remain motionless during the automatic measurements every 30 min during waking hours of the day while pursuing their normal activities. The arithmetic mean of all daytime measurements was calculated and designated as ambulatory BP. Only those recordings with at least 75% of the preset daytime measurements available for analysis were accepted and included in the final evaluation.

Urinary albumin concentration was measured by the immunoturbidimetric method. Using the mean of measurements at the end of the wash-out phase, normoalbuminuria was defined as an albumin / creatinine ratio of < 2.27 mg / mmol creatinine, microalbuminuria as a ratio of 2.27 to 22.7 mg / mmol creatinine, and clinical proteinuria as a ratio of > 22.7 mg / mmol creatinine. All laboratory measurements were performed centrally by an independent institution (Viollier, Basle, Switzerland).

Statistical Analysis Data management and analysis were performed by an independent company (Brunner and Hess, Zürich, Switzerland). Descriptive statistics were based on absolute and relative frequencies, counts and mean values with standard deviations for the groups and subgroups to be considered, as well as scatter plots of bivariate distributions with their respective regression lines. Calculation of *P* values for the rejection of zero hypothesis was performed with nonparametric test procedures (Wilcoxon pairwise and Wilcoxon-Mann-Whitney groupwise). Results are presented as means ± SEM.

RESULTS

Part 1: Ambulatory BP, Office BP and Albuminuria in the Untreated Patients At the end of the wash-out period, an ambulatory BP profile meeting the set quality criteria (see above) could be obtained in 54 patients (Table 1). Mean daytime ambulatory BP averaged 147 /

TABLE 2. AMBULATORY OR OFFICE BLOOD PRESSURE AND ALBUMINURIA IN DIABETIC PATIENTS

Patients	No.	Blood Pressure (mm Hg)		Urinary Albumin/Creatinine Ratio (mg/mmol)
		Office	Ambulatory†	
All	54	156*/97 ± 3/2	147/98 ± 2/2	39 ± 12
Normoalbuminuria	21	154/99 ± 4/3	145/100 ± 4/3	1.3 ± 0.1
Microalbuminuria	23	155/93 ± 4/2	147/96 ± 3/2	8.1 ± 1.1
Clinical proteinuria	10	162/100 ± 4/2	152/100 ± 4/3	159 ± 39

Values are means ± SEM.

* $P < .05$ *versus ambulatory systolic blood pressure.*

† *Mean of daytime values*

98 ± 2/2 mm Hg and office BP 156/97 ± 3/2 mm Hg (Table 2). Forty-nine patients (91%) were considered hypertensive based on ambulatory BP measurements (mean daytime diastolic BP, ≥ 85 mm Hg) and 37 patients (69%) had office hypertension (office diastolic BP, > 90 mm Hg). Urinary albumin excretion was normal in 21 patients (39%). Twenty-three patients had microalbuminuria (43%) and 10 clinical proteinuria (19%). There was no significant difference in ambulatory or office BP among these three subgroups. However, systolic BP was higher ($P < .05$ for all patients) when measured by a physician than during ambulatory monitoring in patients with normoalbuminuria or microalbuminuria as well as in those with clinical proteinuria.

The difference between office BP and the mean of ambulatory BP was calculated in each patient. Figure 1 depicts the relationship between this parameter (on the ordinate) and the BP reading taken by the physician (on the abscissa), both for systolic (upper panel) and diastolic (lower panel) BP. The sign of the difference between office and ambulatory BP is positive when BP is higher in the presence than in the absence of the physician, the converse being true when the sign of the difference is negative. Despite significant correlations between the two parameters for both systolic ($r = 0.58$, $P < .001$) and diastolic ($r = 0.37$, $P < .01$) BP, the scatter of the individual values was clearly too large to allow the prediction of ambulatory BP on the basis of office BP readings.

Due to a non-Gaussian distribution, the natural logarithm of urinary albumin/creatinine ratio was used for regression analysis. Urinary albumin/creatinine ratio was unrelated to either ambulatory or office diastolic BP or systolic BP (Figure 2).

Part 2: Ambulatory BP, Office BP and Albuminuria During Active Treatment Sixty-two diabetic patients fulfilled the inclusion criteria at the end of the 4-week wash-out phase and underwent the protocol of the active treatment period. Eleven of these patients withdrew during this phase because of side effects (n = 5), non–drug-related intercurrent illnesses (n = 3), antihypertensive inefficacy (n = 1), or merely at their own wish (n = 2). Therefore, 51 patients completed the study (Table 1) and could be analyzed for efficacy. Sixteen patients had previously not received antihypertensive therapy. Of the remaining 35 patients, 12 had been on a β-blocker, 13 on a diuretic, 13 on an ACE inhibitor, 5 on a calcium antagonist, and 2 on other agents. These drugs, given either as mono- or combined therapy, were all withdrawn before the 4-week run-in phase.

During wash-out conditions, 19 (37%) patients had normoalbuminuria, 23 (45%) microalbuminuria, and 9 (18%) clinical proteinuria (Table 3). On active treatment, office BP decreased progressively, although in the clinical proteinuria subgroup this was delayed be-

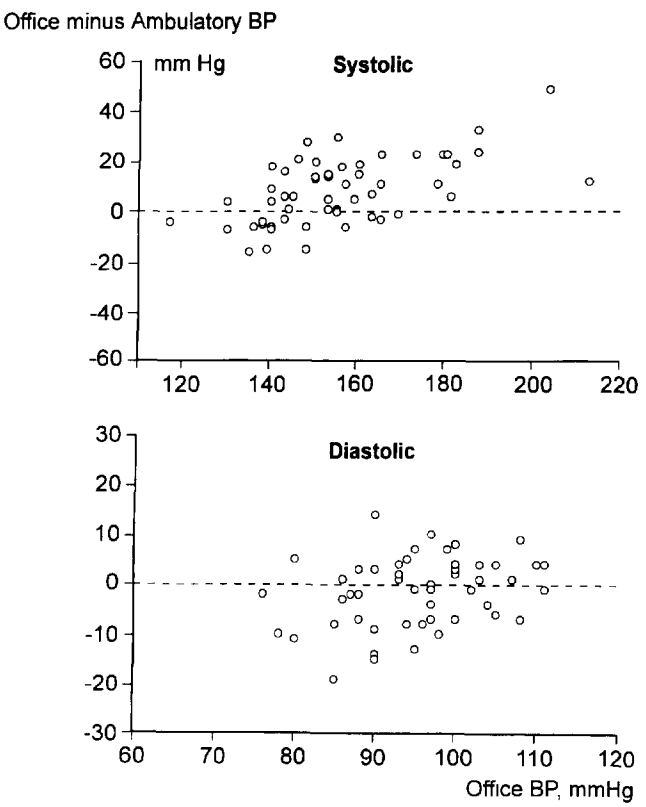

FIGURE 1. *Difference between office and ambulatory blood pressure (Office-Ambulatory BP) plotted against the corresponding office blood pressure (***upper panel** *for systolic and* **lower panel** *for diastolic) in patients with type II diabetes mellitus.*

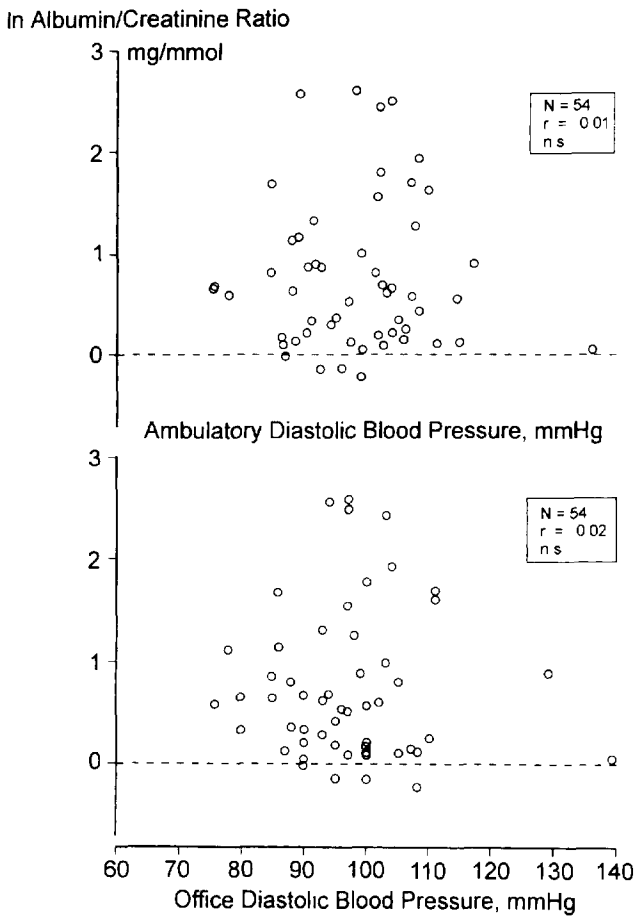

FIGURE 2. *Relationship between diastolic ambulatory blood pressure or office blood pressure (on the abscissa) and the natural logarithm (ln) of the urinary albumin/creatinine ratio (on the ordinate) in patients with type II diabetes.*

yond the 10th treatment week (Table 3). Compared with the wash-out phase, changes in BP after 30 to 40 weeks of therapy did not differ significantly between the albuminuria subgroups. Thus, mean BP (ie, diastolic BP + systolic BP + diastolic BP/3) was lowered from 120.6 ± 2.8 mm Hg to 103 ± 1.9 mm Hg ($P < .0005$, −13.5%) in the patients with normoalbuminuria, from 114.6 ± 2.7 mm Hg to 106.4 ± 1.7 mm Hg ($P < .005$, −6.6%) in those with microalbuminuria, and from 120.1 ± 2.7 mm Hg to 106.3 ± 3.1 mm Hg ($P < .01$, −11.4%) in those with clinical proteinuria.

Considering subgroups with different drug treatments, mean BP decreased in the cilazapril monotherapy group (n = 14), representing 28% of patients, from 114.3 ± 2.7 mm Hg after wash-out to 102.7 ± 2.8 mm Hg ($P < .01$, −9.6%) after 30 to 40 weeks of active therapy. In the ACE inhibitor calcium antagonist group (n = 11), accounting for 22% of the patients, mean BP was not improved after the initial 10 weeks of cilazapril monotherapy (117.2 ± 3.3 mm Hg *v.* 118.5 ± 2.4 mm Hg after wash-out), but decreased to 105.0 ± 2.4 mm Hg ($P < .01$, −10%) at the end of the subsequent cilazapril–amlodipine combination phase. In the triple therapy group (n = 17), mean BP tended to decrease only minimally after the initial cilazapril monotherapy (from 124.1 ± 3.6 mm Hg to 117.2 ± 3.3 mm Hg), averaged 113.5 ± 2.3 mm Hg ($P < .005$, −8.1%) after the subsequent 10-week cilazapril–amlodipine combination phase and decreased further to 108.2 ± 1.4 mm Hg ($P < .0005$, −7.8%) after the addition of hydrochlorothiazide.

With regard to heart rate and body weight, no significant difference was observed at baseline between the three groups, and no significant change was seen later during the course of the study (not shown).

Compared with the wash-out phase, active treatment did not modify the urinary albumin/creatinine ratio in initially normoalbuminuria patients (n = 19), but distinctly reduced this variable in patients with microalbuminuria (n = 23, $P < .05$, on average −24.3 ± 8% at treatment weeks 30 to 40). In those with clinical proteinuria (n = 9), the reduction (−29.4%) was highly variable from patient to patient and did not achieve a significant level. In all hyperalbuminuric patients taken together (n = 32), the reduction achieved −25.7% (from 54 ± 18 mg/mmol to 40 ± 16 mg/mmol, $P < .005$) (Table 3).

Considering groups with different drug treatments, the urinary albumin/creatinine ratio in the patients receiving cilazapril monotherapy (n = 14) decreased from 12.3 ± 5.9 mg/mmol during wash-out to 9.5 ± 4.8 mg/mmol (−22.8%) at treatment weeks 30 to 40 (P = not significant). In the ACE inhibitor calcium antagonist combination group (n = 11), urinary albumin/creatinine ratio decreased from 43.6 ± 31.1 mg/mmol during wash-out to 28.7 ± 17.7 mg/mmol (−34.1%) after the initial 10 weeks on cilazapril alone, and decreased further to 15.8 ± 8.2 mg/mmol (−63.7%) during the subsequent cilazapril–amlodipine combination phase. In the triple therapy group (n = 17), the urinary albumin/creatinine ratio decreased from 60.5 ± 29 mg/mmol to 47.9 ± 23.4 mg/mmol (−20.8%) within the initial 10 weeks of cilazapril therapy, but returned to 57.2 ± 30 mg/mmol (−5.4%) at completion of the trial.

After 30 to 40 weeks of active therapy, there was no significant correlation between urinary albumin/creatinine ratio and mean systolic ambulatory BP (r = 0.01), and systolic office BP (r = 0.01). The same was true for diastolic ambulatory and office BP (r = 0.02 and r = 0.02, respectively). Treatment-associated percentage changes in urinary albumin/creatinine ratio did not correlate significantly with concomitant changes in mean ambulatory and office systolic BP (r = 0.31 and r = 0.01, respectively), as well as with changes in ambulatory and office diastolic BP (r = −0.08 and r = 0.19, respectively).

The effects of active treatment on humoral parameters are shown in Table 4. No significant change was

TABLE 3. EFFECT OF ACTIVE TREATMENT ON OFFICE BLOOD PRESSURE (mm Hg) AND URINARY ALBUMIN/CREATININE RATIO (mg/mmol)

	No.	Baseline	Active Treatment		
			Week 10	Week 20	Weeks 30–40
Blood pressure					
Patients with:					
Normoalbuminuria	19	157/102 ± 4/3	142/94 ± 5/3(‡/†)	137/89 ± 4/3(‡/‡)	137/88 ± 3/2(‡/‡)
Microalbuminuria	23	154/ 95 ± 5/2	147/88 ± 4/2(*/†)	141/90 ± 3/4(†/†)	147/86 ± 4/2(*/‡)
Clinical proteinuria	9	163/ 99 ± 5/2	161/99 ± 7/3(NS/NS)	146/92 ± 5/3(*/*)	144/88 ± 6/3(†/†)
Urinary albumin/creatinine ratio					
Patients with:					
Normoalbuminuria	19	1.2 ± 0.1	1.4 ± 0.2(NS)	1.6 ± 0.2(NS)	1.4 ± 0.2(NS)
Microalbuminuria	23	7.1 ± 1.0	6.4 ± 1.3(NS)	4.7 ± 0.8(†)	5.4 ± 1.0(*)
Clinical proteinuria	91	171 ± 48	127 ± 35 (NS)	143 ± 55 (NS)	128 ± 48 (NS)

* P < .05; † P < .01; ‡ P < .001, NS = nonsignificant versus baseline
Values are means ± SEM.

observed during the course of the study in patients with normoalbuminuria as well as in those with microalbuminuria or clinical proteinuria. There were also no significant changes in the treatment groups, except for a slight increase in serum glucose on hydrochlorothiazide-containing triple therapy (10.68 ± 0.84 mmol/L *v* 9.19 ± 0.69 mmol/L after washout, $P < .05$).

Five patients discontinued the study because of adverse symptoms such as dry cough (n = 3), a rash appearing during the cilazapril monotherapy phase (n = 1), or tiredness and depression reported during the cilazapril–amlodipine combination phase (n = 1).

Intercurrent diseases, leading to study discontinuation but rated as drug unrelated, included myocardial infarction, kidney tumor, and amputation of a foot, each in 1 patient.

DISCUSSION

The findings of this study demonstrate that in type II diabetic patients with hypertension and/or hyperalbuminuria, large differences exist between BP measured in the physician's office and mean daytime ambulatory BP, and that the scatter of individual values of both systolic and diastolic BP was clearly too large to allow the prediction of ambulatory BP on the basis of office BP readings. Moreover, contrasting with the known close correlation between urinary albumin excretion rate and systemic arterial BP in diabetes mellitus type I,[11,13] the level of albuminuria in 54 type II diabetics receiving no antihypertensive therapy was found to be unrelated to either office or ambulatory BP. Complementing this, treatment with the ACE inhibitor cilazapril alone or combined with amlodipine improved both hypertension and hyperalbuminuria.

The presence of diabetes mellitus combined with hypertension or hyperalbuminuria represent a very high risk situation.[4–8] Therefore, diabetic patients deserve careful evaluation and monitoring of their BP and albuminuria state. This trial was performed by practicing physicians, thus reflecting closely the expe-

TABLE 4. EFFECTS OF ACTIVE TREATMENT ON HUMORAL PARAMETERS

		Normoalbuminuria	Microalbuminuria	Clinical Proteinuria	All Patients
Glycosylated hemoglobin (%)	Before	6.9 ± 0.3	7.5 ± 0.3	7.2 ± 0.4	7.3 ± 0.2
	After	6.8 ± 0.4	7.7 ± 0.4	7.7 ± 0.3	7.4 ± 0.2
Serum fructosamine (μmol/L)	Before	293 ± 16	315 ± 113	77 ± 18	300 ± 9
	After	278 ± 14	319 ± 14	285 ± 17	299 ± 9
Serum glucose (mmol/L)	Before	8.6 ± 0.6	10.0 ± 0.7	10.8 ± 1.3	9.5 ± 0.5
	After	9.3 ± 0.7	9.8 ± 0 7	10.3 ± 1.2	9.7 ± 0.5
Serum creatinine (μmol/L)	Before	89 ± 3	92 ± 4	94 ± 4	96 ± 2
	After	85 ± 2	93 ± 4	96 ± 2	91 ± 2
Serum cholesterol/HDL	Before	4.2 ± 0.4	4.8 ± 0.3	5.8 ± 1.0	4.8 ± 0.3
	After	4.2 ± 0.4	4.7 ± 0.3	5.5 ± 0.8	4.7 ± 0.3
Serum, triglycerides (mmol/L)	Before	2.0 ± 0.3	2.0 ± 0.3	3.3 ± 1.1	2.3 ± 0.3
	After	2.2 ± 0.5	2.6 ± 0.6	4.7 ± 2.0	2.9 ± 0.5

Means ± SEM.

rience accumulated by most doctors in taking care of diabetic patients. Moreover, complementing the conventional BP measurements by the physician, BP during everyday activities was monitored whenever possible using the ambulatory recorder Profilomat. This fully automated device is known to provide accurate BP profiles.[21] A large body of evidence suggests that BP recorded outside the medical setting correlates better with renal, cardiac, and cerebral injury than BP obtained sporadically by a physician.[15–18,22,23] Therefore, the use of ambulatory BP monitoring seems particularly attractive in diabetic patients.

The pathogenesis of hyperalbuminuria as a characteristic although not specific manifestation of microvascular renal disease is thought to involve hereditary, metabolic, and hemodynamic factors.[9,10,24,25] Intraglomerular pressure and flow, rather than systemic BP, is the ultimate hemodynamic determinant of glomerular damage.[10] Therefore, the tendency for a close albuminuria–BP relationship in untreated type I diabetics[11,13,22] and the lack of such a correlation in type II diabetics, suggests a different impact of systemic BP on intraglomerular pressure. Thus, in diabetes mellitus type I, where systemic BP increases slightly before or at the onset of nephropathy, afferent arteriolar vasodilation may allow even such mild systemic BP changes to produce parallel increases in intraglomerular pressure. In contrast, in type II diabetics arterial hypertension often precedes diabetes mellitus or nephropathy,[14,26] but may have a less direct effect on intraglomerular pressure. Regardless of the exact systemic–intrarenal pressure relationships, increases in systemic BP are likely to promote, although not necessarily initiate, hyperalbuminuria and nephropathy progression in diabetes mellitus type I as well as type II.[2,27]

The antiproteinuric efficacy of antihypertensive drugs has been shown to differ among certain agents or drug classes.[19,20] Thus, an antiproteinuric effect of diuretics, β-blockers, and several calcium antagonists (except nifedipine, which is ineffective) requires a concomitant reduction in systemic arterial BP. In contrast, ACE inhibitors exert direct intrarenal effects and, thereby, reduce proteinuria even at an unchanged systemic BP. By inhibiting angiotensin II generation they dilate preferentially the efferent arteriole, thereby decreasing intraglomerular pressure to a level lower than expected from changes in systemic BP per se; moreover, they decrease the glomerular permeability for proteins.[28] Therefore, ACE inhibitors have emerged as the preferred drugs for treating microalbuminuria or clinical proteinuria in diabetic patients.[14] The 26% albuminuria reduction achieved with cilazapril in the hyperalbuminuric diabetics is quite similar to the previously reported efficacy of captopril in doses of 75 to 100 mg/day in type I diabetics with either incipient or clinical nephropathy.[29,30] In type II diabetics, long-term treatment with enalapril reduced the progression from incipient to clinical nephropathy in normotensive as well as in hypertensive patients[31,32]; moreover, in the normotensive diabetics, microalbuminuria was not lowered but rather stabilized by enalapril, whereas it increased progressively on placebo.[31] Because cilazapril also lowered systemic BP, the relative contribution of the latter versus direct intrarenal actions could not be further dissected. In the group of diabetics whose BP was not controlled satisfactorily after 10 weeks of cilazapril monotherapy, 20 weeks of combined treatment with cilazapril and the calcium antagonist amlodipine further decreased albuminuria from −34% to −64%. This complements the previous observation of an additive antiproteinuric action of lisinopril and diltiazem versus verapamil[33,34] and supports the potential usefulness of certain ACE inhibitor calcium antagonist combinations in the treatment of diabetic patients with hypertension and/or hyperalbuminuria.[14,34]

Proteinuria is most likely not an innocent bystander, but may probably per se promote nephropathy progression[35,36] and therefore, requires treatment. Without effective therapy, in 80% to 100% of patients diabetic microalbuminuria will progress to the high-risk state of clinical nephropathy.[2,9] Most important, slowing of diabetic nephropathy progression occurred subsequent to proteinuria reduction, but has never been described with persisting unchanged proteinuria.

Overall, the different antihypertensive drugs used in the present trial were well tolerated. Only five patients interrupted the treatment because of side effects. The therapy had no unfavorable impact on humoral parameters.

In summary, these data demonstrate the antiproteinuric effect of prolonged ACE inhibition with cilazapril in diabetic patients. They also indicate that in type II diabetics, urinary albumin excretion is poorly correlated with BP, whether measured in the physician's office or recorded in the patient's usual environment. Moreover, it appears that the level of diastolic BP is underestimated in some diabetics when the measurement is performed by a physician. Finally, the results show that ambulatory BP cannot be predicted in the individual diabetic patient based on office BP readings.

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